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What's in a Name? "Nuclear Transplantation" and the Ethics of Stem Cell Research

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Introduction

On January 15, 2002, the California State Advisory Committee on Human Cloning released its final report, *Cloning Californians?*, unanimously recommending that "California should not prohibit but should reasonably regulate human non-reproductive cloning" based on the conviction that the "use of this technology offers potential medical and scientific benefits while not raising many of the same concerns as human reproductive cloning."[1] Furthermore, the Advisory Committee recommended that:

> California should regulate all human non-reproductive cloning in the State, public or private. That regulation should do at least three things: a) prohibit the use of pre-embryos after development of the primitive streak, b) ensure that the persons providing cells for this purpose gave informed consent, and c) require that the research be permitted by an approved Institutional Review Board ("IRB").[2]

These recommendations concerning the non-reproductive use of cloning technology seek to balance two important ethical mandates, to cure disease and to respect pre-embryos as a form of human life.

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* Director, Biotechnology and Healthcare Ethics, Markkula Center for Applied Ethics, Santa Clara University. I would like to thank the members of the California Advisory Committee on Human Cloning for the collegial—albeit difficult—conversation in which we engaged from May 1999 to January 2002, especially Tracy Trotter, M.D., with whom I prepared a working document on human non-reproductive cloning for the Committee's consideration. That document served as the basis for the discussion of the science of nuclear transplantation in this paper. I would also like to thank Kristen Koenekamp for her research support. Finally, gratitude is extended to the staff of the Hastings Law Journal for sponsoring a stellar symposium and inviting me to be a part of it.

1. REP. OF THE CAL. ADVISORY COMMITTEE ON HUM. CLONING, CLONING CALIFORNIANS? 53 HASTINGS L.J. 1145, 1182 (2002), [hereinafter CLONING CALIFORNIANS?].

2. *Id.*

As a member of the Advisory Committee, I supported these recommendations both as a reasoned and reasonable answer to a public policy question and as reflective of the opinion of the majority of Californians as best as it could be discerned. Nonetheless, the Committee's conclusions are a less than complete answer to the parallel ethics question in that they do not adequately account for concerns for social justice and the common good.

In general, discussions about the ethics of non-reproductive human cloning focus on the tension between obtaining stem cells from pre-embryos and the promise these cells hold for tissue engineering, while largely ignoring the larger social context in which biotechnology in general and medical technology in particular evolves. In many cases, this is a warranted, conscious omission. However, I am increasingly concerned that as we rush to grab the brass ring of potential cure heralded by research on non-reproductive human cloning, we have not adequately confronted the healthcare burdens potentially placed on those currently marginalized by American health care.

Although the Advisory Committee discussed the distributive justice question, it deserves deeper public consideration. Ethically sound policy regarding biomedical innovations in California requires looking through the lens of a larger healthcare picture that includes:

- More than 2 million California children (ages 0-18)—7 million Californians total—without any form of health insurance;[3]
- 1.9 million (21%) children—4.7 million Californians total—living in poverty;[4]

3. E. Richard Brown, *California's Growing Uninsured Population and Options to Expand Coverage*, UCLA CENTER FOR HEALTH POL. RES. (May 2000), *available at* http://www.healthpolicy.ucla.edu. The year 1999 is the latest year for which California statistics are available. It is important to note that whereas the uninsured rate of children nationally remained relatively flat (14-15%) nationwide between 1995 and 1998, that of California's children rose from 17% to 21% over the same time period. The current economic downturn does not bode well for increasing the numbers of insured Californian children. In 1999, almost 7 million Californians—20% of the state's inhabitants—were without health insurance of any kind. DEMOGRAPHIC RES. UNIT, ST. OF CAL. DEP'T OF FIN., CALIFORNIA CURRENT POPULATION SURVEY REPORT: MARCH 2000 DATA 10 (2001), *available at* http://www.dof.ca.gov [hereinafter SURVEY REPORT]. Nationwide, the total percent of uninsured persons of all ages from January through June 2001 was 14.1%; the total percent of uninsured persons 18 years and under was 11.2%, probably reflecting the implementation of the State Children's Health Insurance Program (SCHIP). U.S. DEP'T OF HEALTH & HUM. SERVICES, CENTERS FOR DISEASE CONTROL & PREVENTION, NATIONAL HEALTH INTERVIEW SURVEY (2002) *available at* http://www.cdc.gov/nchs/about/nhis/ released200202.htm.

4. *See* SURVEY REPORT, *supra* note 3. The federal poverty line for 1999 was $22,500 for a family of two, $28,300 for a family of three, and $34,100 for a family of four, which is not reflective of the high cost of living in many areas of the state.

- the increasing inability of physicians to obtain vaccines, such as tetanus, for routine administration.[5]

Against this backdrop, I propose to do two things: first, to provide the scientific and ethical background to the recommendations of the Advisory Committee regarding human non-reproductive cloning and, second, to recommend further public policy considerations regarding such research which take serious account of informed choice in the public square and duties to social justice.

I. The Language and Science of Stem Cell Research

A. What's in a Name?

In the Advisory Committee's report, *Cloning Californians?*, the term "non-reproductive human cloning" refers to procedures for "the transfer of human cell nuclei into enucleated oocytes to produce human pre-embryos without implanting the pre-embryos to produce a human child."[6] The Advisory Committee's choice of phraseology was deliberate so as to delineate clearly the use of nuclear transfer "to create early pre-embryos to be used as sources of embryonic stem cells"[7] for research or tissue engineering from the use of this technique to produce a child for rearing. Although the Advisory Committee found the term "non-reproductive human cloning" useful and preferable to "therapeutic cloning,"[8] it now seems prudent to avoid completely the use of the word "cloning" in conversations about the use of somatic cell nuclear transfer to create stem cells.

Bert Vogelstein, chair of the National Academy of Sciences Committee on the Biological and Biomedical Applications of Stem Cell Research, and his co-authors have proposed the term "nuclear

5. *Averting Vaccine Disaster*, WASH. POST, Feb. 22, 2002, at A24. Note that the Centers for Disease Control and Prevention is advising physicians to skip tetanus boosters for teenagers and adults and to prolong the course of diptheria-pertussis-tetanus (DPT) vaccine for babies. At least eight of eleven crucial childhood vaccines are in critical shortage. This is due, at least in part, to the lack of incentives for companies to manufacture vaccines with low profit margins. A drop in immunization rate poses a far greater threat to public health than that created by acts of bioterrorism.

6. CLONING CALIFORNIANS?, *supra* note 1, at 1182. The use of the term "pre-embryo" by the Advisory Committee was also intentional. "Pre-embryo" is short-hand for "preimplantation embryo." In vivo an embryo at this stage of development would not be physically attached to the uterine wall. In the human, implantation typically occurs eight or nine days after fertilization. *See Stem Cells: Scientific Progress and Future Research Directions*, NAT'L INST. OF HEALTH, A-1 (2001) [hereinafter *NIH Stem Cell Report*].

7. *Id.*

8. One reason for preferring "non-reproductive human cloning" to the commonly used "therapeutic cloning" was that there are, to date, no "therapeutic" applications of this technology.

transplantation" for the use of somatic cell nuclear transfer to create stem cells.[9] The term nuclear transplantation "captures the concept of the cell nucleus and its genetic material being moved from one cell to another, as well as the nuance of 'transplantation,' an objective of regenerative medicine."[10] Using the term "nuclear transplantation" could add needed precision to scientific and ethical considerations of stem cell research. There are several reasons why "nuclear transplantation" is better than other terms.

First, language means everything in public deliberation and policy formation about human cloning. In the language of science, "cloning" refers to the various processes used to copy biological material—bacteria, chromosomes, or cells for example. Cloning so understood does not necessarily involve the mechanical transfer of nuclear genetic material from one cell to another or result in the formation of genetically identical organisms.

Second, once out of the laboratory and into the public square, the term "cloning" unfortunately becomes synonymous with using "somatic cell nuclear transfer" for the purpose of creating offspring. For example, legislation currently under consideration in the United States Senate defines "human cloning" as "human asexual reproduction, accomplished by introducing nuclear material from one or more human somatic cells into a fertilized or unfertilized oocyte whose nuclear material has been removed or inactivated so as to produce a living organism (at any stage of development) that is genetically virtually identical to an existing or previously existing human organism."[11]

The bill then prohibits human cloning so defined. Curiously, if enacted, a plethora of experimental protocols would be proscribed—including study of inheritable genetic disease and birth defects—while leaving it permissible to "clone" a human being through embryo splitting.[12]

Third, although there are political reasons for spreading the "cloning" net broadly, it is best to link the term "cloning" solely with the goal of the process, that is, making a copy of biological material, *not* with the procedure used to attain that aim. As Vogelstein and co-authors claim:

9. Bert Vogelstein et al., *Please don't call it cloning!*, 295 SCI. 1237 (2002).

10. *Id.*

11. Human Cloning Prohibition Act of 2001, S. 1899, 107th Cong. § 301 (2001).

12. Early stage embryos can be split in the laboratory in order to produce two genetically identical embryos which if implanted and brought successfully to terms would result in the birth of "identical twins," or "human clones." In equating "cloning" with "nuclear transfer," Senate Bill 1899, the Brownback bill, seemingly allows for "human cloning" via embryo splitting while prohibiting all use of nuclear transfer, even that unassociated with reproduction.

> The goal of creating a nearly identical genetic copy of a human being is consistent with the term human reproductive cloning, but the goal of creating stem cells for regenerative medicine is not consistent with the term therapeutic cloning. The objective of the latter is not to create a copy of the potential tissue recipient, but rather to make tissue that is genetically compatible with that of the recipient... "[T]herapeutic cloning" is conceptually inaccurate and misleading, and should be abandoned.[13]

Finally, although the term "non-reproductive cloning" avoids the pitfall of disguising potential treatments as actual cures, it nonetheless invites confusion between creating a copy of a human and making tissues genetically compatible with a particular human. Paying attention to terminology would help clarify the significant scientific, medical, and ethical distinctions between human reproductive cloning and using nuclear transfer to make stem cells.

B. Somatic Cell Nuclear Transfer and Nuclear Transplantation Therapy

For purposes of this paper, nuclear transplantation is defined as "the transfer of human cell nuclei into enucleated oocytes to produce human pre-embryos without implanting the pre-embryos to produce a human child."[14] It refers to the use of somatic cell nuclear transfer to create embryonic stem cells—initially for research purposes, eventually, it is hoped, for regenerative medical purposes.

Perhaps the most far-reaching potential application of nuclear transplantation is the generation of cells and tissues that could be used for so-called "regenerative medicine." Many diseases and disorders result from tissue destruction or the disruption of cellular function. Today, donated organs, e.g. kidneys, and tissues, e.g. cartilage, are often used to replace ailing or destroyed organs and tissues. Unfortunately, the number of people suffering from organ-destroying disorders far outstrips the number of organs available for transplant. In addition, since donated organs differ genetically from the recipient (unless from an identical twin), powerful drugs must be used to suppress the recipient's immune response. Pluripotent stem cells, obtained from human blastocysts and stimulated to develop into specialized cells, offer the possibility of a renewable source of replacement cells and tissues to treat a myriad of serious conditions for which no curative treatment now exists. These include

13. *See* Vogelstein et al., *supra* note 9.

14. CLONING CALIFORNIANS?, *supra* note 1, at 1182. The Advisory Committee further stipulates that stem cells should be isolated from these pre-embryos only prior to the formation of the primitive streak. *See* U.S. DEP'T OF HEALTH, EDUC., & WELFARE ETHICS ADVISORY BOARD, REPORT AND CONCLUSIONS: HEW SUPPORT OF RESEARCH INVOLVING HUMAN IN-VITRO FERTILIZATION AND EMBRYO TRANSFER, 101 (1979). This developmental stage is also called the blastocyst. *See Research on Preembryos: Justifications and Limitations*, FERTILITY & STERILITY 62S, 63S (1990).

Parkinson's Disease, Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease), Alzheimer's dementia, spinal cord injury, stroke, burns, heart disease, diabetes, retinal degeneration, osteoarthritis, and rheumatoid arthritis, among others.

There is almost no realm of medicine that might not be touched by this innovation. For example, the transplantation of healthy heart muscle cells could provide new hope for patients with chronic heart disease whose hearts no longer pump adequately. The hope is to develop heart muscle cells from human pluripotent stem cells and transplant them into the failing heart muscle in order to augment the function of the increasingly flaccid heart. Preliminary work in mice and other animals has demonstrated that healthy heart muscle cells transplanted into a failing heart successfully repopulate the heart tissue and work together with the host heart cells to restore adequate pumping ability.[15]

Although this research shows extraordinary promise, there is much to be done before the promise is realized. Technological challenges remain before these discoveries can be incorporated into clinical practice. These challenges, though significant, are not insurmountable.

First, the triggers of cell specialization in humans must be better understood in order to reliably and efficiently direct pluripotent stem cells to become the type(s) of tissue needed for transplantation. Second, the mechanisms responsible for the "reversal" of cell specialization following nuclear transplantation must be delineated. Third, before any cells can be used for transplantation, immune rejection must be overcome. Because human pluripotent stem cells derived from embryonic or fetal tissue would be genetically different from the recipient, the transplant might be rejected by the recipient's immune system.[16] Research needs to focus on modifying human pluripotent stem cells to minimize or to eliminate tissue incompatibility or to create cell and tissue banks with the most

15. *See, e.g.*, Donald Orlic et al., *Bone Marrow Cells Regenerate Infarcted Myocardium*, 410 NATURE 701 (2001); A.A. Kocher et al., *Neovascularization of Ischemic Myocardium by Human Bone-marrow-derived Angioblasts Prevents Cardiomyocyte Apoptosis, Reduces Remodeling and Improves Cardiac Function*, 7 NATURE MED. 430 (2001).

16. Some scientists, notably Hans Keirstead of the University of California at Irvine and Robert Lanza of Advanced Cell Technology in Massachusetts, have stated that the need for nuclear transplantation in order to thwart immune rejection has been "overstated." This is especially true in the case of neuro-degenerative conditions such as Parkinson's disease, paralysis, and multiple sclerosis since the central nervous system is "immune privileged." The brain and spinal cord have scant immune protection and tissue transplanted into the central nervous system is less likely to be rejected than tissue transplanted elsewhere, such as in the heart or pancreas. *See* Tom Abate, *Drugs Posited As Stand-in For Stem Cell Cloning*, S.F. CHRON., Mar. 18, 2002, at E1.

common tissue-type profiles.[17] Finally, the long term ability of pluripotent stem cells to divide in culture is unknown. It is important to work out both the molecular mechanism of so-called cellular "immortality" and to discover if this same mechanism could allow cell division to run amuck, potentially resulting not in cure but in cancer.

C. Stem Cells—They're Not Just from Plants Anymore

Human embryological development is a matter of exquisite complexity.[18] Many sorts of laboratory experiments have been designed to study how fertilization occurs and how a fertilized oocyte produces a blastocyst, the first instance of cell specialization. Approximately twenty-four hours after fertilization in vitro, the fertilized egg, or zygote, goes through its first division to produce two identical cells and then splits again to produce four cells. Asynchronous cell division continues producing eight cells, sixteen cells, and so on—each round of cell division taking approximately thirty-six hours.[19] By days five and six post-fertilization, the tightly wound ball of dividing cells develops a cavity. This cell ball is the blastocyst. It is now evident that cells have specialized. The blastocyst has an outer rim of cells—the trophectoderm—and an inner group of cells, the inner cell mass. The cells of the inner cell mass can give rise to all types of bodily tissue as well as some

17. Although a common argument in support of creating blastocysts for research on nuclear transplantation—a line of reasoning used by the Advisory Committee in support of its recommendation on human "non-reproductive cloning"—is the need to create cells and tissues that will not be rejected by the recipient, it seems highly unlikely that specifically creating tissues for each and every potential patient—a number in the hundreds of thousands—will be possible or, indeed, desirable. Simply, it is too expensive, time consuming, and labor intensive to be scalable. Research underway at Geron Corporation, and elsewhere, is focusing on the creation of lines of "null" stem cells which do not possess rejection triggering chemicals on their surface. There is also an effort to genetically engineer stem cells in order to create viable lines of common tissue type profiles. Theoretically, the capacity of stem cells to self-replicate would allow these lines to proliferate indefinitely. Therefore, it might be possible to create tissue banks of both undifferentiated and specialized cells and tissues. Such cell banks might diminish—and perhaps ultimately negate—the need for embryonic and fetal tissue, as the stem cell lines would be self-replicating. Currently, there are banks which store placental and umbilical cord blood, rich sources of blood-forming—or hematopoietic—stem cells, multipotent cells which can develop into oxygen carrying red blood cells, infection fighting white blood cells, and clot promoting platelets. Cells from such banks have been used to treat sickle cell anemia and leukemia.

18. KEITH L. MOORE & T.V.N. PERSAUD, THE DEVELOPING HUMAN: CLINICALLY ORIENTED EMBRYOLOGY 29-34 (W.B. Saunders Co., 5th ed., 1993).

19. *NIH Stem Cell Report*, *supra* note 6, at A-3.

developmentally supportive tissues.[20] The trophectoderm forms part of the placenta.[21]

It is at this stage of embryogenesis that human embryonic stem cells (hES cells) can be derived from the inner cell mass of the blastocyst. Most of the blastocyst cells are in the outer rim with only thirty to thirty-four cells in the inner cell mass.[22] The stem cells in the inner mass are freed from the outer layer and put in culture to be grown in the laboratory. It is hoped that under laboratory conditions, embryonic stem cells can retain two defining characteristics—their ability to divide for indefinite periods (i.e., self-replication) and their capacity to give rise to the more than 200 types of specialized cells making up the human body (i.e., pluripotency) including nerve cells, muscle cells, skin cells, blood cells.[23]

In the laboratory, pluripotent stem cells can be derived from three sources: post-infertility treatment blastocysts, fetal tissue, and somatic cell nuclear transfer techniques.

The first human embryonic stem cells were derived in 1998.[24] In the work done in the laboratory of Dr. James Thomson, pluripotent stem cells were isolated directly from the inner cell mass of blastocysts obtained from infertility clinics. These embryos—originally made for purposes of reproduction, not research—were in excess of the clinical need and voluntarily contributed by the gamete donors. Informed consent was obtained from the donor couples for this research use. Dr. Thomson isolated the inner cell mass from the donated blastocysts and produced a pluripotent human stem cell line.

In contrast, Dr. John Gearhart and colleagues isolated pluripotent stem cells from fetal tissue obtained from terminated pregnancies. Fetal tissue donors gave informed consent after they

20. It is important to note that although embryonic stem cells are pluripotent (i.e., they can develop into all types of body cells), they are not able to generate a body plan or assemble tissues in an ordered way and, hence, cannot, on their own, develop into an embryo. *See, e.g.*, Martin F. Pera, *Human Pluripotent Stem Cells: A Progress Report*, 11 CURRENT OPINION IN GENETICS & DEV. 595, 597-98 (2001).

21. *NIH Stem Cell Report*, *supra* note 6, at A-3.

22. *Id.* at 13.

23. *Id.* at 1. This is not meant to imply that any given stem cell can become all the types—indeed, it seems that it cannot. In addition, stem cells cannot develop into embryos or to entire living organisms any more than an isolated sperm or egg can.

24. Michael J. Shamblott et al., *Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells*, 95 PROC. NAT'L ACAD. SCI. 13726, 13726-31 (1998); James A. Thomson et al., *Embryonic Stem Cells Derived from Human Blastocysts*, 282 SCIENCE 1145 (1998). Thomson and colleagues obtained hES cells from early embryos created in the course of infertility treatments voluntarily donated by the gamete donors. A second method was used by Shamblott and co-workers who isolated human embryonic germ (hEG) cells—which have properties very similar to hES cells—from human fetal tissue obtained from terminated pregnancies. In both instances, informed consent was given for the material to be used in research.

had independently made the decision to end their pregnancy. Dr. Gearhart took cells that were precursors of eggs and sperm. These primordial germ cells were isolated and grown in culture to produce a pluripotent stem cell line. Although the fetal stem cells developed in Dr. Gearhart's lab and the embryonic stem cells developed by Dr. Thomson's lab were derived from different sources, they share many characteristics including long term self renewal, no chromosomal abnormalities, and pluripotency.[25]

Nuclear transfer is a third way that pluripotent stem cells may be created and isolated. The use of somatic cell nuclear transfer techniques to produce viable cloned mammals—of which Dolly was the first[26]—established that egg cytoplasm could reprogram somatic cell genetic material into a state of pluripotency—effectively running the cellular specialization clock backwards. In addition, embryonic stem cells have been isolated from blastocysts created through somatic cell nuclear transfer,[27] the same procedure used to produce Dolly. Because somatic cell nuclear transfer potentially allows the creation of pluripotent stem cells genetically matched to individual patients, it is heralded as a possible method for developing cell-based and tissue-based treatments for degenerative disease and injury.

For example, consider a person with progressive heart failure. In theory, a nucleus from a heart patient's skin cell could be injected into an egg cell whose own nucleus had been removed. Under appropriate conditions, the patient's skin cell nucleus could fuse with the egg cell resulting in the egg behaving as if it had just been fertilized—undergoing cell division and, with time, becoming a blastocyst. Stem cells could be isolated from the inner cell mass and a culture of pluripotent cells created. These cells could then be stimulated to develop into heart muscle cells. Because the vast majority of genetic information is contained in the nucleus, these cells would be essentially identical genetically to the person with the failing heart. When these heart muscle cells were transplanted back into the patient, there would likely be no rejection and no need to expose the patient to immune-suppressing drugs, which can have toxic effects.

Notably, in March of 2002, the first successful use of nuclear transplantation to treat disease in laboratory mice was reported in the

25. *NIH Stem Cell Report, supra* note 6, at 14.

26. I. Wilmut et al., *Viable Offspring Derived from Fetal and Adult Mammalian Cells*, 385 NATURE 810 (1997).

27. *See, e.g.*, Konrad Hochedlinger & Rudolf Jaenisch, *Monoclonal Mice Generated by Nuclear Transfer from Mature B and T Donor Cells*, 415 NATURE 1035 (2002); Teruhiko Wakayama et al., *Differentiation of Embryonic Stem Cell Lines Generated from Adult Somatic Cells by Nuclear Transfer*, 292 SCI. 740 (2001).

journal *Cell*.[28] The experiments involved mice with severe immune deficiency. Dr. Jaenisch and colleagues isolated skin cells from the affected mice. The scientists removed the nucleus from a mouse egg and replaced it with the nucleus of one of the isolated skin cells. The fused egg underwent division forming a blastocyst from which stem cells were isolated. The genetic defect that had made the donor mouse sick was corrected in the stem cells before the cells were chemically molded into precursors of immunity producing cells. Finally, these repaired immune cells were injected into the affected donor mouse restoring immunity.

Although heralded in the press as a harbinger of the treatments to come for human degenerative disease, a caveat is in order. Dr. Jaenisch's group injected 202 enucleated mouse eggs with skin cell nuclei in order to get a single blastocyst from which stem cells could be isolated. Obtaining such a large number of human eggs—perhaps 200 per treated patient—would be expensive, difficult, and quite ethically troubling. However, with remarkably increased efficiency and fewer ethical edges, this method seems to hold promise for cellular repair and tissue regeneration in the clinical context. However, this mouse work itself is quite preliminary and, to date, there have been no reports of successful somatic cell nuclear transfer and blastocyst formation using human cells. Jaenisch's work is an important first step towards regenerative medicine—but it is only the first step of a long, frustrating, exciting journey.[29]

What makes pluripotent embryonic stem cells of interest in tissue regeneration is their ability to undergo further specialization into specific types of "multipotent" stem cells that are committed to give rise to cells that have a particular function. An example of such multipotent cells are hematopoietic stem cells, which give rise to red blood cells, white blood cells, and platelets—and were the precursor

28. William M. Rideout III et al., *Correction of a Genetic Defect by Nuclear Transplantation and Combined Cell and Gene Therapy*, 109 CELL 17 (2002), *available at* http://www.cell.com.

29. In addition to possibly holding the key to restoring bodily function through the replacement of disease affected cells and tissues, there are several additional reasons why the creation and isolation of human pluripotent stem cells is important to science and medicine. At the most fundamental level, research on pluripotent stem cells could provide clarification of the complexities of early human development including: embryogenesis (i.e., embryo formation) and embryopathy (i.e., disorders of embryo formation), the biology of human implantation, and the causes of spontaneous abortion. Furthermore, human pluripotent stem cell research could also dramatically change the way pharmaceuticals are developed and tested for safety. For example, new medications could be initially tested on human pluripotent cell lines. This could streamline the process of pharmaceutical development, as only those compounds found both safe and effective in such cell line testing would graduate to further testing in laboratory animals and human subjects.

cells transplanted into the immune deficient mouse by Jaenisch and colleagues. Like pluripotent stem cells, these more specialized stem cells are important in early human development. Unlike pluripotent cells, multipotent stem cells are found in both children and adults. For example, consider blood, or hematopoietic, stem cells which reside in the bone marrow of every child and adult, and can be found in very small numbers circulating in the blood stream. Blood stem cells perform the critical role of continually replenishing our supply of blood cells—red blood cells, white blood cells, and platelets—throughout life.

There is evidence in mammals that blood stem cells—and other specialized multipotent cells—can change course and produce skin cells, liver cells, or cell types other than a blood stem cell or a specific type of blood cell. For example, experiments in mice suggest that blood stem cells can generate functioning liver cells.[30] Findings such as these suggest that even after a stem cell has begun to specialize, the stem cell may, under certain conditions, be more plastic[31] than first thought.[32]

Research on human adult stem cells suggests that these multipotent cells have both research and therapeutic potential. For example, if adult tissue contains multipotent stem cells which are both self replicating and able to differentiate into a variety of cell types, then they could be isolated from a heart patient, coaxed into dividing, directed into becoming heart cells, and re-introduced into the patient. It is unlikely that they would be rejected since they originated in the patient and no immunosuppression would be required. The use of adult stem cells for such cell therapies could reduce or perhaps negate the use of stem cells from human blastocysts or fetal tissue, sources that trouble some people on ethical grounds.

While adult stem cells hold promise, there are some very significant limitations to what may or may not be accomplished with them. First of all, as previously noted, stem cells from adults have not been isolated for all tissues of the body. Thus far, adult stem cells have been identified in brain, bone marrow, blood vessels, skeletal muscle, cornea, retina, liver, and pancreas.[33] Notably, adult cardiac stem cells or adult pancreatic islet stem cells in humans have not been found. Second, adult stem cells are often present in only minute

30. Eric Lagasse et al., *Purified Hematopoietic Stem Cells Can Differentiate into Hepatocytes Inter Vivo*, 6 NATURE MED. 1229 (2000).

31. "Plasticity" refers to the capacity of some adult stem cells to differentiate into tissues other than the ones from which they originated. *NIH Stem Cell Report*, *supra* note 6, at ES-7.

32. Alan Coleman, *Somatic Cell Transfer in Mammals: Progress and Applications*, 1 CLONING 185 (1999).

33. *NIH Stem Cell Report*, *supra* note 6, at ES-6.

quantities, are difficult to isolate and purify, and their numbers may decrease with age. A significant limiting factor in the potential of adult stem cells in regenerative medicine is the insufficient numbers of cells available for transplant.[34] Finally, current evidence indicates that adult stem cells have a limited capacity to give rise to many different specialized cell types.[35]

Any attempt to use stem cells from a patient's own body for treatment would require that stem cells be isolated from the patient and grown in culture in sufficient numbers for therapeutic use. For some acute disorders, there may not be enough time to grow a sufficient number of cells. In other disorders, caused by a genetic defect, the genetic error would likely be present in the patient's stem cells. In addition, adult stem cells may contain genetic abnormalities, caused by daily living and by "errors" made in gene replication during the course of a lifetime.[36] These potential weaknesses could limit the usefulness of adult stem cells.

Although there has been great enthusiasm in the media over the isolation of stem cells, the case can be overstated.[37] Consider, for example, the fervor over the claim of Anthrogenesis Corporation to have derived "embryonic stem cells" from placenta.[38] Notably, articles describing the research including the use of cell markers to confirm that these cells are stem cells—either pluripotent or multipotent—have not been published. Stem cells may have been isolated from placenta, but what type and what is their capacity to differentiate into other cells types? It is a mistake at this point to think of placental derived cells as replacements for embryonic stem cells or to conclude that no further research is needed with pluripotent cells or other multipotent cell types.

Absent sufficient evidence that adult stem cells have the broad potential characteristic of pluripotent stem cells, it is prudent to study the developmental capability of adult stem cells alongside that of pluripotent stem cells. It is too early to say whether one type of stem cell or the other will prove best for a given disease or injury; but it is probably reasonable to say that one cell type will not be sufficient for all regenerative needs. It may be that stem cells from adult tissue will

34. *Id.*

35. *Id.* at ES-9 to ES-10.

36. Andrew J.G. Simpson, *The Natural Somatic Mutation Frequency and Human Carcinogenesis*, 71 ADVANCES IN CANCER RES. 209, 227-31 (1997).

37. This is a trap into which reports on either adult or embryonic stem cells can tumble. There is a political agenda at work that tends to obfuscate the actual costs, benefits, and potentialities of both adult stem cell and embryonic stem cell research in the interest of persuasive rhetoric.

38. Nicholas Wade, *A New Source for Stem Cells is Reported*, N.Y. TIMES, Apr. 12, 2001, at A25.

prove useful in the treatment of some diseases, fetal stem cells for others, and embryonic stem cells for others. It is simply too soon to tell. The answers lie in the research ahead.

Scientifically, it seems prudent at this time to proceed—albeit with caution—to: (1) determine the optimal conditions for isolation and culture of both human embryonic and adult stem cells; (2) define which particular diseases are best treated by pluripotent stem cells and which by multipotent stem cells; and, (3) discover the factors which will induce stem cells—both pluripotent and multipotent—to differentiate into the desired cell type, e.g., neurons or heart cells. In parallel, animal models can: (1) supply data for optimizing human cell experiments; (2) address safety concerns, both in tissue development and in transplantation; and, (3) assess the outcomes of using stem cell transplants for given diseases and injuries.

II. The Ethics and Public Policy of Nuclear Transplantation and Stem Cell Research

A. "What's in the Dish?"

Embryonic stem cell science in general, and the making of blastocysts through nuclear transfer in particular, raises cavernous limit questions—questions of ethics which science cannot, indeed ought not, answer. The prime area of ethical disquiet is the question of the moral status of human blastocysts.[39] Is a human blastocyst a new person whose life merits protection, or an emergent being without tangible interests and unable to make a strong moral claim for protection, or is a human blastocyst something else entirely?[40] The argument for full protection is predicated on considering the human blastocyst as a full human person possessing the full moral rights and protections of personhood. Hence, any action resulting in direct harm to the blastocyst may not be undertaken even in pursuit of the goods of human health. In contrast to the full personhood view is the developmental view of moral status, which posits that a human acquires interests, rights, and roles incrementally as sentience, consciousness, and relationships develop and justify these safeguards. On this view, the blastocyst may be accorded respect and value, but

39. The moral status of the blastocyst was a primary area of ethical inquiry for the Advisory Committee. Other ethical concerns regarding "non-reproductive cloning" considered by the Committee were: risk/benefit analysis, the slippery slope, potential exploitation of egg donors, and distributive justice. *See* CLONING CALIFORNIANS?, *supra* note 1, at 1183-89.

40. This concern is not unique to nuclear transplantation of course. Any type of work using human embryos—from treating infertility to studying embryogenesis to deriving stem cells—raises the moral status question.

can be destroyed for good reason. Finally, perhaps the blastocyst created and housed in a laboratory has no claim to either full or developing moral status, as there is no potential ex utero to develop into a child. McGee and Caplan have labeled this dilemma as the "what is in the dish" problem.[41]

Recognizing that embryonic cell status is not a scientific matter, they argue that embryonic stem research itself radically changes the problem of defining basic facts about human embryos. For example, the very isolation of human gametes and blastocysts from their biological environments causes these cells to "take on different meanings, depending on the institutional context."[42] For example, in the medical context, frozen sperm, eggs, and embryos can become "treatments" for infertility or "property" to be awarded in divorce or probate proceedings. In creating blastocysts in the laboratory—whether potentially to treat infertility or potentially to treat heart failure—cells that were once of use only within the human body have become of use outside of that context. Hence, whatever moral status blastocysts may have in the body may be only an "indicator" of their status "in the dish." This is further complicated by the changing nature of the cells in the dish.

> The changing nature of what is in the dish is obvious. It was not long ago that Western society and particularly the United States debated the status of ordinary embryos. At that time, the single-cell human embryo was fairly well understood to be the product of conception, and its ordinary end, birth. Today, stem cells, gametes, embryos, and tissues from humans and animals can be combined in unusual ways without conception, and potentially brought to birth. . . . [T]he point here is that we can in no way infer what ought to be done with these new technologies from a scientific analysis of embryo or fetal development. What an embryo or fetus is, is changing.[43]

Not only can an "ought" not be derived from an "is," what in fact "is" is in flux. McGee and Caplan suggest a move away from the developmental view of moral status and an engagement in public conversation about the changing nature of human reproduction and the changing definition of "reproductive material."[44]

But, although patently necessary, public engagement does not seem enough. Ethics requires raising the question behind the question. The moral status "answer" is given to the "what's in the dish" question. However, the prior question—the question behind

41. Glenn McGee & Arthur L. Caplan, *What's in the Dish?*, 29 HASTINGS CENTER REP. 36, 37 (1999).

42. *Id.*

43. *Id.* at 38.

44. *Id.*

the question—is why are we worried about the contents of the dish in the first place? Are we once again seeking to discover what makes us human and to lay claim to that? Are we troubled by the abortion question or the possibility of germ-line genetic engineering? Are we afraid of "playing God?" Are we lured by hopes of human health and well-being? Are we fulfilling mandates to heal and to care?

And, in infinite regression, there are questions behind these questions: Is there good to be gained, right to be done, harm to be avoided, promises to be kept, justice to be meted out? Not knowing just what a blastocyst is leaves duties towards these entities hazy and ill-defined. There seems to be an assumption that once the moral status of the embryo is clearly defined what is to be done will be unmistakable. Perhaps—but it is not likely. Indeed, there is moral myopia inherent in allowing the dish dilemma to be the sole arena of inquiry regarding nuclear transplantation. First, it reflects a general fascination with the ethics of the "materials and methods" of research, without imagining the "results and conclusions." It does not engage the question behind the question—the question of what is down the path of inquiry we choose to follow. Who will benefit, and at what cost? Who will be harmed, and at what gain? Will an even deeper trench between the medical haves and have-nots be dug? "No one doubts that [actor and Parkinson's afflicted] Michael J. Fox will receive stem cell therapy should it become available. But will the poor and middle class around the world indeed benefit?"[45] Second, moral myopia cannot, by definition, bring the question behind the question into focus—the question not of what *is* the case, but of what *ought* to be the case. Laurie Zoloth elaborates: "What is at the heart of the issue [of using embryos to create stem cells] is to ask: Are some things so important to human advancement that we have a responsibility to pursue them? Who are we if we turn away, who are we if we proceed?"[46]

B. Promises, Promises

The enormous medical potential of research on stem cells in general and nuclear transplantation in particular is a forceful and persuasive incentive to continue. However, despite all of the promises that the fruits of embryonic and adult stem cell research and nuclear transplantation are ripe for the picking, the primary beneficiaries of regenerative medicine in all likelihood will not be contemporary advocates, Michael J. Fox and paralyzed Christopher

45. Vanessa T. Kuhn, *Stem cells: Equity or Ownership?*, 2 AM. J. OF BIOETHICS 1, 2 (2002).

46. Laurie Zoloth, *Jordan's Banks, A View from the First Years of Human Embryonic Stem Cell Research*, 2 AM. J. OF BIOETHICS 3, 7 (2002).

Reeve, but ill and injured future persons. Sobering as it may be, there are no known once-ill-now-healthy beneficiaries of stem cell and nuclear transplantation research. What is possible today is small, steady down payments on a future that, no matter how bright, is ultimately unknowable.

One of the basic tenants of medical ethics is the right to informed consent. Using understandable language and description, medical professionals are obligated to tell patients the truth about their condition. Truth telling respects autonomy and sets the parameters for informed choice. In cases of life threatening illness, the truth is framed so as to mitigate against unrealistic expectations for cure. For example, a cancer patient ought not to be told that there is a "wonderful chance" of cure with an exotic and burdensome procedure known to succeed in like cases less than 5% of the time. Current stem cell rhetoric hovers dangerously close to violating the public's right to informed consent and choice. Creating false hope is wrong at the bedside and is wrong in the public square. A particularly troubling example is the comments of Michael West, CEO of Advanced Cell Technology, after testifying before an appropriations subcommittee of the Senate in December 2001. West is quoted by *New York Times Syndicate* reporter, Judy Holland, as saying that "a six-month moratorium on human cloning [i.e., nuclear transplantation] could lead to the loss of 3,000 lives a day because that many people die from degenerative diseases that could potentially be treated."[47] This quote illustrates what Rebecca Dresser calls the instigation of "unrealistic optimism."[48] Such overstating of the facts of the matter is wrong because it disrespects the moral agency of patients and the public. It is simply impossible to have off-the-shelf tissue therapies to save a single life—let alone 3,000 lives—within months. To say so is disingenuous at best and intentionally misleading at worst. Either way, it is to be avoided.

If we seek to have a serious, on-going public deliberation about stem cells, nuclear transplantation, and other human biotech innovations, as the Advisory Committee strongly recommends,[49] then the truth about stem cells must be told. Research on stem cells and nuclear transplantation is just beginning.[50] There are no therapies, no cures, no clinical trials. There is potential and there is hope but there

47. Judy Holland, *Biotech Firm Expects to Make Tissue from Stem Cells in Six Months*, N.Y. TIMES SYNDICATE, Dec. 5, 2001, *available at* www.RNAture.com.

48. Rebecca Dresser, *Embryonic Stem Cells: Expanding the Analysis*, 2 AM. J. OF BIOETHICS 40, 41 (2002).

49. *See* CLONING CALIFORNIANS?, *supra* note 1, at 1146, 1191-92.

50. This includes embryonic cells obtained from donated embryos and those obtained after nuclear transplantation as well as adult stem cells. At one time or another all have been oversold to the public.

are no guarantees. It is incumbent on those whom the public views as "experts"—scientists, biotech CEOs, legislators, corporate attorneys, patient advocates, journalists, bioethicists (especially those who consult in the bioscience boardroom)—to do no harm, which counsels truth telling and the avoidance of hype in the public square. Only then can responsive and responsible public conversation ensue as we "come to grips with the new dilemmas posed by rapid advances in our understanding of human biology."[51]

C. Moral Imagination and Social Justice

Moral imagination has been described as "the capacity to empathize with others and to discern creative possibilities for ethical action,"[52] taking sympathetically the perspective of those affected by a decision. In thinking about stem cell research in general and nuclear transplantation in particular, who is it that warrants empathy? Let me suggest that it is not primarily the ill or injured who will potentially benefit in the future from the ripening of the fruits of current research on regenerative medicine—although empathy, understanding, care, and compassion are surely owed to them. However, the prime recipients of our empathic understanding ought to be those who reside on the margins of health care *today*—those without the basics of nutrition and medical care; those whose lives are riddled with violence and abuse; those who have no other voice but ours in the public square. If stem cell technologies are, as has been claimed, the most significant medical breakthrough since sanitation and antibiotics, how can we assure that our empathy embraces those who today lack plumbing and pills?

It is likely that the research necessary in order to realize "the enormous medical promise of stem cells to relieve human suffering"[53] will be expensive. And, if the therapeutic dream comes true, the tissue-based treatments for degenerative disease and injury will be dear. But, even if the cost question is equitably addressed, there is another question lurking behind; that is, whether we ought to consume precious resources—time, money, intellectual energy—on such research when 2 million of California's youngest residents have no consistent access to cough medicine, vaccinations, and antibiotics.

A road taken always leaves a road untrod. Will pursuing the path of regenerative medicine further marginalize those already disadvantaged by the current healthcare (un)system? Does exercising empathy for those on the margins require traipsing a different path or, perhaps, erecting a bridge between high tech research and access

51. CLONING CALIFORNIANS?, *supra* note 1, at 1193.
52. Thomas E. McCollough, THE MORAL IMAGINATION AND PUBLIC LIFE 16 (1991).
53. CLONING CALIFORNIANS?, *supra* note 1, at 1188.

to low tech health care? Note that I am not suggesting that stem cell and nuclear transplantation research be forfeited—the promise is simply too great. What I am suggesting is that the down payment on the future of stem cells is due and payable today to those living on the margins of health, especially children.

Moral imagination asks not only for empathy but also for imaginatively perceiving opportunities for acting.[54] One such opportunity would be to construct a health care vision for the state, one that includes the health and well-being of every Californian.[55] Such a vision would, first, provide a justice-based framework for deciding to what extent to pursue particular biotech innovations[56] and, second, guarantee that those who have no other voice but ours are heard and benefited by the road taken.

Conclusion

The ethical concerns regarding nuclear transplantation and embryonic stem cell research are not exhausted by a consideration of moral status. I have raised two other areas of concern—informed consent in the public square and social justice. There are others.

It is not merely stem cell science that is complex. Stem cell ethics is—as is the green ogre Shrek[57]—complex "like an onion"[58] with layer upon layer upon layer of questions. I have modestly proposed these two for your consideration.

54. *See* MARK JOHNSON, MORAL IMAGINATION: IMPLICATIONS OF COGNITIVE SCIENCE FOR ETHICS 202 (1993).

55. A national health care vision is also sorely needed but there is a profound lack of political will on the issue of health and health care.

56. For a discussion of "clone age justice," see Margaret R. McLean, *Much Ado About Cloning in the Public Square*, 32 U. TOL. L. REV. 337, 347-49 (2001).

57. SHREK (DreamWorks 2001).

58. *Id.*